SUMMARY STATEMENT
(Privileged Communication)

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Release Date: 08/11/2004

Application Number: 1 U01 NS048122-01A1

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Review Group: NSD-C
Neurological Sciences and Disorders C

Meeting Date: 06/09/2004
Council: OCT 2004
Requested Start: 01/01/2005

RFA/PA: PAR02-139
PCC: PORTELCN

Project Title: Therpeutic Interventions in Peripheral Neuropathy

SRG Action: Priority Score: 207 Percentile: 36.6
Human Subjects: 10-No human subjects involved
Animal Subjects: 30-Animals involved - no SRG comments or concerns noted

Project Year	Direct Costs Requested	Estimated Total Cost
1	521,205	684,460
2	523,907	688,008
3	558,274	733,140
4	683,072	897,028
5	838,314	1,100,896
TOTAL	3,124,772	4,103,531

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1U01NS048122-01A1 Glass, Jonathan

RESUME AND SUMMARY OF DISCUSSION:

This is the resubmission of a U01 grant application that proposes to further characterize the calpain inhibitor, AK295, and produce sufficient pre-clinical data to seek its approval as a treatment for human neuropathies. Although there was general agreement that the U01 mechanism had been addressed, considerable discussion was generated by this application. The reviewers generally agreed that fundamental issues were not clearly presented or understood with regard to the use of the calpain inhibitor and neuropathies, particularly given that calpain has been shown to be beneficial in the treatment of human neuropathies. Thus, a more systematic approach to testing this compound would significantly improve the reviewer's enthusiasm for this application.

DESCRIPTION (provided by applicant):

Peripheral neuropathies (PN) constitute a major category of neurological disease causing progressive numbness, pain, and weakness in millions of people worldwide. The sequelae of peripheral neuropathy result in significant neurological morbidity, and billions of dollars spent in direct medical costs and loss of productivity. Peripheral neuropathy is also the most frequent neurotoxic side effect of chemotherapeutic agents, resulting in dose reduction or cessation of otherwise effective cancer therapies. Chemotherapy induced peripheral neuropathy (CIPN), like many other neuropathies, is characterized by degeneration of axons. Axonal degeneration is associated with activation of calcium-activated cysteine proteases, calpains. Inhibition of calpains prevents axonal degeneration in experimental models. We developed a clinically relevant animal model of peripheral neuropathy caused by administration of Taxol, a commonly used chemotherapeutic drug for solid cancers. Mice treated with Taxol develop a sensory neuropathy typical of the human condition. Systemic administration of an experimental calpain inhibitor, AK295, prevents Taxol neuropathy in both short and long term studies. The broad, long-term objective of this proposal is to further characterize AK295 and develop enough pre-clinical data in order to seek approval as a treatment for human neuropathies. The Aims are to 1) develop ELISA and HPLC/mass spec assay methods to measure blood and tissue levels of AK295, 2) optimize the dose and schedule of AK295 for prevention of neuropathy, and test the oral bioavailability of AK295, 3) assure that AK295 will not interfere with the primary anti-cancer effects of Taxol, and 4) prepare an IND application for the FDA for testing AK295 in humans. An additional Aim will be to test our library of other calpain inhibitors and calpain inhibitors from the literature, comparing them to AK295 for efficacy, toxicity, and bioavailability. Successful completion of these Aims will provide a potential treatment for neuropathy where no current treatment now exists. We also believe that this approach to prevention of neuropathy may have broad reaching relevance to other human peripheral neuropathies.

CRITIQUE 1:

SIGNIFICANCE: The goal of this project is to conduct a series of preclinical studies on the experimental calpain inhibitor, AK295, as a means of evaluating its potential as a drug for preventing chemotherapy-induced peripheral neuropathy (PN). PN is a common side effect observed in the treatment of breast cancer patients with Taxol. Therefore, the identification of a drug that can effectively reduce PN while not interfering with the primary anti-cancer effects of Taxol, and other cancer chemotherapeutic agents known to cause PN, would represent an important improvement in the treatment of cancer. Since PN is also observed in a variety of other diseases, including diabetes mellitus, HIV infection, and other types of cancer chemotherapy, the results of this study may lead to a treatment strategy that extends beyond the treatment of breast cancer.

APPROACH: The research described in this grant application is makes a good attempt at meeting the goals of the program announcement, which is aimed at studies necessary to begin the testing of a drug that is of importance to the clinical mission of the NINDS. In the original grant application, the P.I. provided interesting preliminary data regarding the ability of the peptide analog, AK295, to reduce taxol-induced peripheral neuropathy. Preliminary data was also provided to demonstrate that the team of investigators has an interesting pipeline of compounds that can also be evaluated for their efficacy in reducing taxol-induced PN. There are five specific aims in this revised grant proposal. The first specific aim focuses on the development of a series of analytical methods for evaluating the in vivo properties of AK295. This includes the development of HPLC methods for determining the enantiomeric purity and stability (i.e., epimerization of the Aby residue in AK295) in vivo, as well as the development of ELISA and LC/MS methods for metabolite analysis. The second specific aim involves evaluating the pharmacokinetics of AK295 using different routes of administration. This includes comparing subcutaneous and oral routes of administration. These specific aims are unchanged from the original grant application. The goal of the third specific aim is look at the ability of AK295 to prevent taxol-induced PN using the different routes of administration. The P.I. has added a series of studies to assure that AK295 does not interfere with the anticancer effects of taxol. This addition to Specific Aim 3 was done in response to concerns raised during the initial review of this proposal. Specific Aim 4 involves a series of in vitro screens aimed at identifying new calpain inhibitors that work as well or better than AK295. The analogs that will be evaluated will come from a compound library reported by Dr. Powers, the Co-P.I. of this project, in the Journal of Medicinal Chemistry in 1996. The investigators have also revised this specific aim to include a comparison of their compounds with other calpain inhibitors that are in the literature, with the ultimate goal of identifying compounds that may have a better therapeutic potential than AK295. Specific Aim #5 involves the GMP synthesis of 50-100 g of AK295 that will be needed for the toxicity studies.

Although the proposed research contains some strong points, there are a number of concerns regarding the in vivo properties of AK295, and its structural congeners, that diminish the level of enthusiasm for this grant proposal. Many of these concerns were identified in the initial review of this application and the P.I. has done an insufficient job in this revised application to ease these concerns.

The first and major concern is the ability of AK295 to cross an intact cell membrane and inhibit calpain in vivo. It was pointed out in the previous review that AK295 has a 1000-fold lower potency in the cell culture assay versus the in vitro enzyme assay (Table on page 51). The P.I. has provided lipophilicity calculations for AK295 and its structural congeners, and some analogs (i.e., 18, 19, and 35) have higher calculated log P values and are predicted to have greater membrane permeability than AK295. The P.I. also suggests that we should not prejudge these compounds until their oral bioavailability is determined. Unfortunately, the investigators have missed the point this reviewer was attempting to make. That is, the data shown in the Table given on page 51 of the grant proposal clearly shows that analogs 18, 19 and 35 have a similar or poorer IC_{50} in the cell permeability assay versus that of AK295, yet they have a lower IC_{50} in the enzyme assay and more optimal log P values. Why is this so? Based on the rationale described in Li et al., 1993, assay platelet membrane permeability assay is a valid method for determining the ability of a small molecule inhibitor to cross an intake cell membrane inhibit calpain II-mediated cleavage of the cytoskeleton protein, spectrin. If compounds 18, 19, and 35 cannot cross an intact platelet membrane, they are not likely to cross the membrane of a neuron and prevent PN regardless of the improvement in oral bioavailability they are predicted to have over AK295. Another point that was mentioned in the resume of this application and not addressed at all by the P.I. was the marginal protective effect AK295 appears to have in the taxol neuropathy mouse model (Figures 1 and 2). This marginal effect is likely related to the poor cell permeability of this class of compounds, which is a common feature of peptide-based enzyme inhibitors. The concentration of 50 □M concentration needed in the cell culture assays to demonstrate and effect in Figure 3 only adds further support that these compounds are likely to have a marginal effect in preventing PN in vivo.

A second concern has to do with the organization of the specific aims. Why are the investigators putting so much effort in years 1-3 in evaluating AK295 in the bioavailability and metabolism assays,

when in the second half of year 3 they will begin evaluating new compounds that may work better than AK295? The P.I. claims on page 43 of the application that they can screen additional compounds in their library very quickly in their cell culture and animal models. Why wait until year 3 to do this. The logic presented on page 65 is not very convincing given the concerns about AK295 identified above.

A third concern has to do with statements made on page 66 of the grant application regarding the licensing of AK295 to Cortex Pharmaceuticals. What is the status of the intellectual property regarding AK295? Does Cortex have an interest in pursuing clinical studies with this compound, or have they abandoned it in lieu of something else? This is an important issue since there is no point in proceeding with the evaluation of AK295 as a potential drug if the company with exclusive rights to it has no interest in pursuing it, but can block its use at a later date because it is a competitor to another drug they have in development.

MILESTONES: The P.I. has identified a clear list of tasks and milestones on page 45 of the grant application. However, it is not clear why the P.I. is starting the evaluation of new compounds in year 3 of the grant and not in year 1, since the data regarding the effectiveness of AK295 in vivo is not overwhelming.

INVESTIGATORS: The P.I. and Co-P.I. lead a strong team of investigators and are very capable of conducting the research described in this project.

ENVIRONMENT: Adequate for the proposed research project.

PROTECTIONS: No concerns.

DATA AND RESOURCE SHARING: No data and resource sharing plan was provided. This point was made in the initial review and not addressed by the P.I.

BUDGET: The P.I. has requested $360,000 ($60,000 for consultants and $300,000 for toxicity studies) for the collection of data leading to an IND submission. However, a quick review of the fee schedule listed on page 12 of the application indicates that the low end costs of taking AK295 up to the IND preparation and submission stage is ~$740,000. The high end cost (i.e., using the upper value in the price estimates) is $1,500,000. On what basis did the P.I. come up with the amount of $360,000 for the IND-enabling studies?

CRITIQUE 2:

RESUME: This U01 re-application proposes to further characterize AK295 and develop enough pre-clinical data to seek approval for using AK295 to block chemotherapy induced peripheral neuropathy. In addition, the PI will test a library of other calpain inhibitors and calpain inhibitors from the literature, comparing them to AK295 for efficacy, toxicity, and bioavailability.

SIGNIFANCE: The proposed studies address important question concerning how chemotherapy induced peripheral neuropathy (CINP) can be reduced. CINP occurs frequently and can limit the dose of chemotherapy the patient can receive so CINP can impact both quality of life and survival of the patient.

APPROACH: The overall approach taken by the PI is sound although what appears to be missing is a systemic approach to assessing specificity, bioavailability, toxicity, tumorigenic potential and other potential CNS and peripheral side effects. As the PI is proposing to examine not only AK295 along with a variety of other calpain inhibitors and presumably any candidate that would move forward to human clinical trials would need to pass the above screens. While some of these are included in the revised application the application still appears to take an ad hoc approach to evaluating the compounds'

actions in these assays vs. adopting a more rigorous screening procedure that would weed out potential candidates that have an unwanted side effect profile. Providing such a systematic approach to assessing potential calpain inhibitors that would be efficacious in attenuating CIPN would significantly strengthen the application.

Specific Aims: This proposal outlines a strategy for translating their animal-based discoveries regarding calpains and peripheral neuropathy into new therapies for preventing peripheral neuropathies in humans. In the majority of peripheral neuropathies the pathologic process leading to neurologic dysfunction is axonal degeneration. Over the past 10 years investigations in this laboratory have shown that activation of the cysteine protease calpain is a major cause of axonal degeneration in peripheral neuropathy. Based on these findings, a collaboration was initiated between the principle investigators of this grant proposal, a neurologist/neuroscientist and an enzyme biochemist, in order to test the hypothesis that inhibition of calpains will protect against axonal degeneration and neuropathy. The data, generated in an animal model of chemotherapy-induced peripheral neuropathy (CIPN), indicates that their hypothesis is correct. There are currently no treatments available for preventing axonal degeneration or peripheral neuropathy, and the PI and his colleagues believe that their novel calpain inhibitor AK295 may be the first drug to fill that essential need.

This Translational Research proposal describes the PI's approach to characterizing the effectiveness, pharmacokinetics, and potential toxicity of the anti-neuropathy drug AK295. Simultaneously, this group will develop a second generation of AK295 analogs with improved pharmacokinetic parameters, particularly oral bioavailability. Successful completion of this project will provide the necessary data to move into Phase I trials of AK295 to prevent human CIPN.

Aim 1: Develop an assay method for measuring blood and tissue levels of calpain inhibitors. The plan is to develop both ELISA and HPLC/Mass Spec *assays* for AK295 that will allow the quantitation of drug levels in blood and tissues. As other appropriate candidate drugs are identified (Aim 4), assay methods will also be developed for these other drugs.

Aim 2: Measure the pharmacokinetics of AK295. The PI will use the assay methods from Aim 1 to measure blood and tissue levels of AK295 in the mouse model of Taxol-induced peripheral neuropathy as treated by continuous subcutaneous dosing. The efficacy of AK295 is already established in this model. The plan is to measure oral bioavailability of AK295, test multiple different single doses and measure blood, tissue, and urine levels of AK295 as well as the clearance of the drug with the aim of maintaining a 24-hour level equal to continuous subcutaneous dosing.

Aim 3: Optimize the treatment of Taxol-induced neuropathy in the mouse model. The established treatment model may not represent the optimum in terms of dosing schedule and route of administration. The PI proposes to determine whether AK295 needs to be administered throughout the observation period following Taxol exposure, or just at the time of Taxol exposure. If AK295 is orally bioavailable they will test its efficacy in the Taxol model after oral dosing. In addition they will use cytotoxicity assays and cancer models to assure that AK295 will not interfere with the anti-cancer effects of Taxol. Preliminary toxicity studies of AK295 in mice will be performed.

Aim 4: Identify new candidate drugs for treatment of PN by in vitro screening methods. Available ketoamide calpain inhibitors will be tested for efficacy in peptide-AMC assays, cytotoxic cell culture assays, and then by toxic neuropathy assays in DRG cultures. A few selected compounds (1 or 2 per year) with good therapeutic profiles will be chosen for further development. All of these compounds will be compared with calpain inhibitor compounds from the literature. The goal is to choose a drug that may have a better therapeutic profile than AK295.

Aim 5: Submit an application to the FDA for clinical trials with AK295. An IND application will be prepared and the PI will contract for the GMP synthesis of 50 - 100 grams of AK295. They will also

complete a library of toxicity studies with GMP material. If necessary they will repeat animal efficacy studies with GMP material.

The major strength of the application are the data Dr. Glass has already generated showing that AK295 can attenuate Taxol induced peripheral neuropathy as assessed using both histological and a behavioral measurements (rotorod performance). In the previous review there were several concerns raised by the reviewers. The first major concern was regarding the *in vivo* properties of AK295 and its structural congeners and, in particular, its oral bioavailablity. The PI has responded that other commercial drugs such zidovudine, cyclosporine, and omeprazole have a similar bioavailablity profile as AK295. Immediately before this review, the PI provided a set of data showing that the PI has screened a number of new calpain inhibitors for their ability to inhibit Taxol-induced calpain activity in PC12 cells. Thus, twelve ketoamides (including AK295) and 8 epoxides were screened. Two of the compounds were further tested for their protective effect in the PI's DRG model of chemotherapy-induced peripheral neuropathy and the PI reports that these compounds show significant protection and should be tested in the whole animal model. It was not clear from this last update whether these compounds were to take the place of AK295 given the above concerns of the bioavailability of AK295, but the PI stated that funding from this proposal will allow his group to actively pursue testing of other compounds and large-scale synthesis of those that are most promising.

A second concern in the previous application was the potential for interaction between AK295 and the primary chemotherapeutic agent, possibly interfering with the tumoricidal effect of the chemotherapy. To address this concern a section has now been added which includes measurements of cell death using Taxol with or without AK295 on a breast cancer cell line (MDA MB 231), which demonstrates no interference of AK295 with the effects of Taxol on these cells. The PI will also develop an *in vivo* assay in nude mice, following the protocol of Martin, et al. (Martin, Parr et al. 2003) where breast cancer cells (MDA MD 231) will be implanted and allowed to proliferate subcutaneously, and then treated with Taxol. Tumor regression will be monitored simultaneously with the development of neuropathy, and the effect of AK295 both on the neuropathy and tumor regression will be measured. This study will be complicated, but is an essential milestone before testing this agent in humans. While this data will be useful, it is not clear why the PI has also not included other tumors such as ovarian and lung where Taxol remains first line therapy. These cells are available from NCI and are used by nearly all groups who are screening drugs for effects on tumor cell growth. This issue of calpain inhibition affecting tumor cells is an important one, not only because different tumor cells may respond differently to a particular calpain inhibitor, but because the number of mammalian calpain family members has grown to 14 on last count. Since there is already an extensive literature on calpain's involvement in cancers and some of the calpains have been reported to be tumor suppressors (calpain 9) it will be extremely important to have more thorough assays, utilizing a variety of tumor cell types (in particular lung, ovary and breast which is treated with paclitaxel), to determine the effects that any of the proposed inhibitors may have on tumor cell growth.

A third concern is behavioral assessment of neuropathy in these animals. Previously rotorod, SNAP and histology measures of CIPN were provided and the PI has now added tail-flick assessment to monitor sensory function. While these tests may be of some use in assessing CIPN for the most part they do not mirror the behavioral manifestations of CIPN that is observed in humans. In humans with CIPN, thermal hyperalgesia to heat is rarely observed whereas cold hyperalgesia or allodynia is quite common. Similarly, in the great majority who experience CIPN following paclitaxel administration report myalgias and arthralgias (thought to be mediated by damage to large diameter nerve fibers) as opposed to sensory disturbances associated with C-fibers. In light of these clinical observations, the grant would be significantly strengthened if the PI could include data showing that they can quantitatively assess behavioral measures that more closely mirror the behaviors observed in human patients with CIPN.

A fourth concern is that it is difficult to understand how AK295 or new calpain inhibitors are to be systematically assessed for; potency in reducing CIPN, specificity, bioavailability, toxicity, tumorigenic

potential and other potential CNS and peripheral side effects. The PI is proposing to examine not only AK295 but a variety of other calpain inhibitors. Presumably, any candidate calpain inhibitor that would move forward to human clinical trials would need to pass the above screens. While some of the necessary screens are included in the revised application there still appears to be an ad hoc approach to evaluating potential compounds in these various assays vs. adopting a more rigorous and weighted screening procedure. By adopting a weighted screening procedure the PI may be able to weed out potential candidates that have a highly unwanted side effect profile at an early rather than late stage and thus focus on promising candidates that have a real chance of making it to and through the clinical testing phase. Providing such a systematic approach to assessing potential calpain inhibitors that would be efficacious in attenuating CIPN would significantly strengthen the application.

INNOVATION: The techniques outlined by the PI are not particularly innovative as calpain inhibitors have been around for well more than a decade. What is innovative about this proposal is that the PI is attempting to develop a therapy for treating a condition that currently has only non-mechanism based therapies in place to deal with the CINP long after it has been induced.

INVESTIGATOR: Dr. Glass is a neurologist at Emory and received excellent training in the clinical understanding and assessment of peripheral neuropathies at Johns Hopkins University

ENVIRONMENT: While the general research environment at Emory University is excellent for the proposed studies.

BUDGET: The budget appears to be high given the relatively limited number of experiments that are proposed.

ANIMAL WELFARE: The use of animals is clearly justified as it is the only approach currently available to experimentally determine the mechanisms that give rise to CIPN.

CRITIQUE 3:

SIGNIFICANCE: Peripheral neuropathies (PN) constitute a major category of neurological disease causing progressive numbness, pain, and weakness. The sequelae of peripheral neuropathy result in significant neurological morbidity, and billions of dollars spent in direct medical costs and loss of productivity. Peripheral neuropathy is also the most frequent neurotoxic side effect of chemotherapeutic agents, resulting in dose reduction or cessation of otherwise effective cancer therapies. Chemotherapy induced peripheral neuropathy (CIPN), like many other neuropathies, is characterized by degeneration of axons. Axonal degeneration is associated with activation of calcium-activated cysteine proteases, calpains. Inhibition of calpains prevents axonal degeneration in experimental models. The PI has developed a clinically relevant animal model of peripheral neuropathy caused by administration of Taxol, a commonly used chemotherapeutic drug for solid cancers and will use this model to further characterize AK295 (a calpain inhibitor) and develop enough pre-clinical data in order to seek approval as a treatment for human neuropathies.

APPROACH: This is a revised application. The research described in this grant application is appropriate for the program announcement to establish a cooperative agreement under the NINDS program in translational research for the purpose of identifying calpain inhibitors as a putative candidate for the treatment of Taxol-induced peripheral neuropathies. In this application, the PI has provided compelling preliminary data regarding the ability of the peptide analog, AK295, to reduce Taxol-induced peripheral neuropathy. The PI has other compounds that can also be evaluated for their efficacy in reducing induced-induced PN. Four specific aims are described in this project. The first specific aim focuses on the development of a series of analytical methods for evaluating the in vivo properties of AK295. This includes the development of HPLC methods for determining the enantiomeric purity and stability (i.e., epimerization of the Aby residue in AK295) in vivo, as well as the development of ELISA

and LC/MS methods for metabolite analysis. The second specific aim involves evaluating the pharmacokinetics of AK295 using different routes of administration. This includes comparing subcutaneous and oral routes of administration. The third specific aim is essentially a continuation of Specific Aim 2, but involves looking at the ability of AK295 to prevent induced-induced PN using the different routes of administration. Specific Aim 4 involves a series of *in vitro* screens aimed at identifying new calpain inhibitors that work as well or better than AK295. The analogs that will be evaluated will come from a compound library reported by Dr. Powers, the Co-PI of this project.

INNOVATION: The proposal is innovative and clinically relevant.

INVESTIGATOR: Dr. Glass is highly qualified to carry out the proposed studies.

ENVIRONMENT: Emory University is an excellent environment for Dr. Glass to successfully complete the studies in this application and possibly come up with the treatment of Peripheral Neuropathy.

OVERALL EVALUATION: This is a revised application and is much improved since its first submission. The PI has addressed the concerns raised by previous reviewers: 1) The PI has added Dr. Fanucchi, a clinical oncologist as requested by a reviewer; 2) To provide support for the difference in Ki (41 nM) and IC50 (45μM) values of AK295, the PI has given examples of commercial drugs (zidovudine, cyclosporine and omeprazole) with similar values to AK295; 3) The PI agrees that the compounds they are developing may be effective in other neuropathies as stated by reviewers; 4) The breast cancer cell line described in the original proposal is MDA MB 231and the PI proposes to use this line both *in vitro* and *in vivo*; and 5) Finally, the PI has also added the tail-flick assessment to monitor sensory function and has updated the reviews on calpain inhibitors to address concerns raised in the last review. Furthermore, the PI's supplemental data demonstrates the bioavailability of AK295 1 hour after intravenous injection and generation of new candidate drugs for Peripheral Neuropathy (PN). Dr. Glass has addressed all the concerns raised in the last review and successful completion of these studies would produce compounds with therapeutic application in PN.

HUMAN SUBJECT: No concerns.

ANIMAL WELFARE: No concerns.

ADDITIONAL DISCUSSION:

1. Potential deleterious effect of calpain inhibition is not considered. The literature suggests a potential neuroprotective effect of calpain against apoptosis by cleavage of procaspase 3 thereby inhibiting the caspase 3-dependent apoptosis (J Biol Chem 278: 43245-43253, 2003). It may be necessary to expand the cell type to include neuronal cells to study for this potential undesirable effect of calpain inhibition. The experiments need to look for a potential sensitization to apoptosis and not just cell survival under a non-stressed condition.

2. Is the fact that AK295 is sufficiently antigenic to successfully generate antibody a problem? Will antibody produced in humans accelerate the elimination and null whatever pharmacokinetic data that can be obtained from naïve animals? If antibody is readily produced, PK studies in sensitized animals may be necessary.

3. Selective protection against large fiber degeneration will limit the use of calpain-inhibitors for treating various predominantly small-diameter neuropathies such as those associated with painful diabetes and AIDS neuropathies.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMAL (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested. However, there was some confusion regarding the proposed budgetary needs and the expected results. The applicants are encouraged to provide a more detailed explanation of the requested budget.

NOTICE: The NIH has modified its policy regarding the receipt of amended applications. Detailed information can be found by accessing the following URL address: http://grants.nih.gov/grants/policy/amendedapps.htm

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in $25,000 modules, without budget detail for individual categories. Further information can be obtained from the Modular Grants Web site at http://grants.nih.gov/grants/funding/modular/modular.htm

MEETING ROSTER

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